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Pyridine and Pyridine Derivatives High Production Volume (HPV) Chemical Category

Assessment of Data Availability and Test Plan

Prepared for:
The American Chemistry Council's
Pyridine and Pyridine Derivatives HPV Work Group

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Introduction

In accordance with the United States Environmental Protection Agency (U.S. EPA) High Production Volume (HPV) Challenge Program, the Pyridine and Pyridine Derivatives Work Group (Work Group) of the American Chemistry Council is sponsoring a category of chemicals that include pyridine and its derivatives. The Work Group is comprised of the following companies: Koei Chemical Co., Ltd.; Nalco; Nepera; and Reilly Industries, Inc.

As a participant in the U.S. EPA HPV Challenge Program, the Work Group has prepared this Assessment of Data Availability and Test Plan report for its category of chemicals in accordance with guidance provided under the Chemical Right-to-Know Initiative. The Work Group is committed to minimizing the numbers of animals tested under this program.

Pyridine and pyridine derivatives are industrial solvents and chemical intermediates used in the production of drugs and vitamins, as well as industrial products such as paints, dyes, rubber products and adhesives. They also are used in agricultural products including herbicides, insecticides, fungicides and plant growth regulators. Pyridine and pyridine derivatives share many of the same physical, chemical and toxicological properties as other solvents.

Definition of the Pyridine and Pyridine Derivatives Structure-Based Category

The Pyridine and Pyridine Derivatives Category is comprised of nine chemicals with unique Chemical Abstract Service Registry Numbers (CAS RNs; see Text Table A). The Pyridine and Pyridine Derivatives Category consists of the following structurally closely-related types of chemicals: piperidine, pyridine, methyl and alkyl derivatives of pyridine, and nitriles of pyridine. The Pyridine and Pyridine Derivatives Category CAS RNs and chemical names are provided in the following table:

Text Table A: CAS RNs and Chemical Names

CAS RN	Chemical Name
110-89-4	Piperidine
110-86-1	Pyridine
108-89-4	4-Picoline (4-methylpyridine)
108-99-6	3-Picoline (3-methylpyridine)
109-06-8	2-Picoline (2-methylpyridine)
68391-11-7	Pyridine, alkyl derivs.
68909-18-2	Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides
100-54-9	Nicotinonitrile
100-70-9	Picolinonitrile

Structural Information for the Pyridine and Pyridine Derivatives Category Chemicals

The following table presents the molecular formula and molecular weight data for the seven chemicals with defined structures. Pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) are TSCA Unknown, of Variable Composition, or of Biological Origin (UVCB) chemicals, which have unspecified molecular formulas and molecular weights. The defined or representative structures for the Pyridine and Pyridine Derivatives Category chemicals are provided in Table 1 located at the end of this document.

Text Table B: Molecular Formula and Molecular Weight of Chemicals with Defined Structures

CAS RN	Name	Molecular Formula	Molecular Weight
110-89-4	Piperidine	$C_5H_{11}N$	85
110-86-1	Pyridine	C_5H_5N	79
108-89-4	4-Picoline	C_6H_7N	93
108-99-6	3-Picoline	C_6H_7N	93
109-06-8	2-Picoline	C_6H_7N	93
100-54-9	Nicotinonitrile	$C_6H_4N_2$	104
100-70-9	Picolinonitrile	$C_6H_4N_2$	104

Rationale for the Pyridine and Pyridine Derivatives Structure-Based Category

The Pyridine and Pyridine Derivatives Category chemicals are included as a single HPV chemical category based on the following similarities:

- Closely-related structural and functional features;
- Similar or predictable measured and modeled physical properties;
- Similar or predictable measured and modeled biodegradability;
- Similar or predictable measured and modeled environmental fate and toxicity;
- Similar or predictable measured mammalian toxicity; and
- Similar use and disposition patterns.

All members of the Pyridine and Pyridine Derivatives Category are structurally-related derivatives of pyridine in that they are based on the pyridine unsaturated ring structure. Piperidine (CAS RN 110-89-4) is simply the saturated ring structure derivative of pyridine. Although metabolism is not an endpoint for the HPV SIDS, some comments on the metabolism and elimination of pyridine and piperidine are warranted. The metabolism of both compounds is discussed in the chapter on "Heterocyclic Nitrogen" compounds in *Ethel Browning's Toxicity and Metabolism of Industrial Solvents* (Reed, 1990a,b).

Piperidine is a natural constituent of human urine (Von Euler, 1945) and is excreted by humans at a rate ranging from 3 – 20 mg/day in the urine (Reinhardt and Brittelli, 1981). Piperidine is readily absorbed through the gastrointestinal tract, skin and lungs (HSDB, 1988). Rabbits

excrete piperidine unchanged following an injected dose (Hildebrandt, 1900). When piperidine was injected intraventricularly in rats, it disappeared exponentially with a half-life of 20 minutes (Meek, 1974). In another study with rats, most of an i.p. dose of [^{3}H]-piperidine was excreted unchanged (Okano *et al*., 1978). Two major detoxification mechanism metabolites were identified as 3- and 4-hydroxypiperidine, and two unidentified metabolites were assumed to be conjugates. Metabolic studies of analgesics and anesthetics containing the piperidine ring demonstrated the occurrence of *N*-hydroxylation, formation of a 6-oxo-derivative and *C*-oxidative ring cleavage (Oelschlager and Al Shaik, 1985).

Pyridine (CAS RN 110-86-1) is readily absorbed through the gastrointestinal tract, skin and lungs, and is eliminated via the urine, feces, skin and lungs as the parent compound and as metabolites (Jori *et al.*, 1983). Elimination is rapid and there appears to be no tissue accumulation (Jori *et al.*, 1983). Known urinary metabolites of pyridine in mammals include: pyridine *N*-oxide, *N*-methyl pyridine, 4-pyridone, 2-pyridone and 3-hydroxypyridine (Damani *et al*., 1982). The rat has been shown to excrete 70% of a 1 mg/kg dose in the urine in the first 24 hours after dosing (D'Souza *et al*., 1980).

In summary, both piperidine and pyridine are readily absorbed through the gastrointestinal tract, skin and lungs, and eliminated primarily via the urine. Although they do not have a common metabolite, both chemicals have been shown to undergo metabolism via *C*- oxidation and *N*-oxidation, and *N*-methylation has been shown to be a metabolic route for pyridine. Therefore, piperidine would be expected to be metabolized and eliminated in a similar manner and rate as pyridine.

2-Picoline (CAS RN 109-06-8), 3-picoline (CAS RN 108-99-6), 4-picoline (CAS RN 108-89-4), pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) are structurally-related derivatives of pyridine (CAS RN 110-86-1) in that they are based on the pyridine unsaturated ring structure. The structures of these category chemicals are provided in Table 1. 2-Picoline (CAS RN 109-06-8), 3-picoline (CAS RN 108-99-6) and 4-picoline (CAS RN 108-89-4) are simple monomethyl derivatives of pyridine. Pyridine, alkyl derivs. (CAS RN 68391-11-7) is the complex combination of (short-chain) polyalkylated pyridines derived from coal tar distillation or as high-boiling distillates approximately above 150 degrees C from the reaction of ammonia with acetaldehyde, formaldehyde or paraformaldehyde. Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS No. 68909-18-2), in addition to being based on the pyridine unsaturated ring structure, is a dissociable salt (i.e. it is not a chlorinated compound). The cationic nature of this compound allows one to predict that it will be relatively toxic to aquatic species (EPA OPPT, 2002), but is expected to be relatively nontoxic to mammalian species. Published literature demonstrating side-chain oxidation and ring hydroxylation of alkyl-substituted pyridines is available (Hawksworth and Scheline, 1975; Wong, 1990; El-Hraiki, 1990; Kelly, 1990) and is germane to the understanding the common pathways of metabolism and elimination of 2-picoline (CAS RN 109-06-8), 3-picoline (CAS RN 108-99-6), 4-picoline (CAS RN 108-89-4), pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2).

Nicotinonitrile (CAS RN 100-54-9) and picolinonitrile (CAS RN 100-70-9) are structurally-related derivatives of pyridine (CAS No. 110-86-1) in that they are based on the pyridine unsaturated ring structure, but with nitrile substitution instead of alkyl substitution. Hawkins (1988) provides numerous examples of biotransformations of drugs and chemicals based on the pyridine ring structure. These drugs and chemicals have higher molecular weights and contain more complex functional groups than the members of the Pyridine and Pyridine Derivatives Category. The biotransformation pathways indicate that even these higher molecular weight and more complex pyridine derivatives are readily metabolized and predominantly eliminated in urine.

Available Data to Fulfill HPV Screening Information Data Set (SIDS) Endpoints

Approach to Evaluate the Database for the Pyridine and Pyridine Derivatives Category

The following approach was used to obtain and analyze data relevant to the assessment of the Pyridine and Pyridine Derivatives Category.

1. The chemical names and CAS RNs of the nine Pyridine and Pyridine Derivatives Category chemicals supported by the American Chemistry Council Pyridine and Pyridine Derivatives Work Group were provided.
2. Published and unpublished reports were obtained as available from the members of the ACC Pyridine and Pyridine Derivatives Work Group and other sources; they were organized and reviewed to identify studies that could fulfill SIDS endpoints.
3. Pertinent publicly available databases[a] were searched and all reports considered relevant were obtained to establish the full extent and nature of the published literature for the nine Pyridine and Pyridine Derivatives Category chemicals.
4. A references database was developed and maintained in order to track reports through the review, assessment and summarization process.
5. Each of the reports obtained was reviewed to determine adequacy according to EPA criteria and reliability according to Klimisch *et al.* (1997).
6. Robust Summaries were prepared for each report with a Klimisch score of 1 or 2, according to the guidelines proposed by the EPA (U. S. EPA, 1999a) for each study type.
7. Estimates were developed for physical/chemical properties, and environmental fate and ecotoxicity data by using appropriate Quantitative Structure Activity Relationships (QSARs) (U. S. EPA, 1999b).
8. Fugacity modeling (Level III) was performed to estimate transport and distribution into environmental compartments for the Pyridine and Pyridine Derivatives Category chemicals (U.S. EPA, 2000e; Mackay *et al*., 1996a,b).

[a] Databases include ChemIDplus, HSDB (Hazardous Substances Data Bank), IRIS (Integrated Risk Information System), CCRIS (Chemical Carcinogenesis Research Information System), GENE-TOX, EMIC (Environmental Mutagen Information Center), DART/ETIC (Developmental and Reproductive Toxicology and Environmental Teratology Information Center), MEDLINE, TOXLINE, RTECS (Registry of Toxic Effects of Chemical Substances),TSCATS (Toxic Substances Control Act Test Submissions), and the 1996 IUCLID (International Uniform Chemical Information Database).

Use of Structure Activity Relationships for the Pyridine and Pyridine Derivatives Chemical Category

Approaches recommended in the EPA document on the use of structure activity relationships (SAR) in the HPV Chemicals Challenge Program were employed in the assessment of the Pyridine and Pyridine Derivatives Category (U. S. EPA, 1999b). Several models were employed to support the review and assessment of the Pyridine and Pyridine Derivatives Category chemicals. The models included several based on structure-activity relationships (SAR), as well as Mackay-type fugacity-based modeling. The SAR models for physical properties were used to estimate boiling points, melting points, aqueous solubilities, octanol/water partition coefficients and vapor pressures. Other SAR models were used to estimate hydroxyl radical mediated atmospheric photo-oxidation and biodegradation potential. SAR models also were used to obtain estimates of acute toxicity to aquatic organisms.

Common Features of the Models

All of the models (except the Mackay-type models) require the input of a molecular structure to perform the calculations. The structure must be entered into the model in the form of a SMILES (Simplified Molecular Input Line Entry System) notation or string. SMILES is a chemical notation system used to represent a molecular structure by a linear string of symbols. The SMILES string allows the program to identify the presence or absence of structural features used by the submodels to determine the specific endpoint. The models contain files of structures and SMILES strings for approximately 100,000 compounds, accessible via CAS RNs. SMILES strings cannot be developed for mixtures or chemicals without a single, defined structure.

Estimation of Physical/Chemical Properties

The SAR models for estimating physical properties and abiotic degradation (Estimation Programs Interface for Windows, Version 3.10 or EPIWIN v.3.10) were obtained from Syracuse Research Corporation (2000) (U.S. EPA 2000d,f,g). The models were used to calculate melting point, boiling point, vapor pressure (submodel MPBPWIN), octanol/water partition coefficient (K_{ow}) (submodel KOWWIN), and aqueous solubility (submodel WSKOWIN). The calculation procedures are described in the program guidance document and are adapted from standard procedures based on analysis of key structural features (Meylan and Howard, 1999a,b,c).

Estimation of Environmental Fate Properties

Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (U.S. EPA, 2000a). The estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson and co-workers (Meylan and Howard, 2000a). The SAR methods rely on structural features of the subject chemical. The model calculates a second-order rate constant with units of cm^3/molecules-sec. Photodegradation based on atmospheric photo-oxidation is in turn based on the rate of reaction (cm^3/molecules-sec) with hydroxyl radicals (HO•), assuming first-order kinetics and an HO• concentration of 1.5 E + 6 molecules/cm^3 and 12 hours of daylight. Pseudo first-order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2} = 0.693/[(k_{phot} \times HO\bullet) \times (12\text{-hr}/24\text{-hr})]$.

Biodegradation potential was estimated using the submodel BIOWIN (U.S. EPA, 2000b). BIOWIN estimates the probability for the rapid aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. Estimates are based on fragment constants that were developed using multiple linear and nonlinear regression analyses (Meylan and Howard, 2000b). BIOWIN uses the probabilities to estimate a potential pseudo first-order half-life for aerobic biodegradation of the subject chemical in surface water, soil and sediment.

Estimation of Environmental Distribution

The Level III Mackay-type, fugacity-based models were obtained from the Trent University's Modeling Center. The specific model used was the generic Equilibrium Concentration Fugacity model (EQC) Level III, version 1.01 (U.S. EPA, 2000e). These models are described in Mackay *et al*. (1996a,b). Fugacity modeling is based on the "escaping" tendencies of chemicals from one phase to another. For instance, a Henry's Law constant calculated from aqueous solubility and vapor pressure is used to describe the "escape" of a chemical from water to air or vice versa as equilibrium between the phases is attained. Key physical properties required as input parameters into the model are melting point, vapor pressure, K_{ow} and aqueous solubility. The model also requires estimates of first-order half-lives in the air, water, soil and sediment. An additional key input parameter is loading of the chemical into the environment.

Estimation of Acute Aquatic Toxicity

Models developed by the U. S. Environmental Protection Agency (EPA) were employed to make estimates of acute toxicity to aquatic organisms, specifically a commonly tested fish, the fathead minnow (*Pimephales promelas*), a water column dwelling invertebrate (*Daphnia magna*) and a commonly tested green alga (*Selenastrum capricornutum)*. The models are incorporated in a modeling package called ECOSAR, version 0.99g (U. S. EPA, 2000c). ECOSAR may be obtained from the EPA website for the Office of Pollution Prevention and Toxics, Risk Assessment Division. The models calculate toxicity based on structural features and physical properties, mainly the K_{ow} (Meylan and Howard, 1998).

Experimental Database Retrieval

MPBPWIN is designed to search a database of experimental melting point, boiling point and vapor pressure values, and to display these values when found. MPBPWIN generates a "structure representation" for each SMILES entry and then searches the database for a matching "structure representation." A "structure representation" produces a database match if there is an exact atom-to-atom connection match. The experimental values are taken from SRC's PHYSPROP Database. MPBPWIN uses melting point and boiling point values from the database to predict vapor pressure; however, when the user enters his/her own melting point and boiling point values, these values are used instead of the values from the experimental database.

Modeling Information Specific to the Pyridine and Pyridine Derivatives Category

The models described above were used for the Pyridine and Pyridine Derivatives Category chemicals. Estimations of physical properties, environmental fate and distribution, and ecotoxicity data were not possible for two chemicals (CAS RNs 68391-11-7 and 68909-18-2) of the nine HPV chemicals in the Pyridine and Pyridine Derivatives Category because they do not have single defined structures and/or were not available in the files of structures of the models.

The model did not provide estimates of stability in water for this class of chemicals because the model cannot calculate this parameter for chemicals that do not meet the criteria of neutral organic compounds with structures that can be hydrolyzed. For fugacity modeling, all chemical release or input to the environment was assumed to be into air using the chemical specific parameters to attain estimates of the chemical distributions between environmental compartments. Robust Summaries for QSAR Estimates are provided in Appendix B and the modeling results are summarized in Tables 2 through 4.

Physical/Chemical Properties QSAR Estimates and Correlation to Reliable Data

The available reliable data and QSAR estimates for physical/chemical properties of the Pyridine and Pyridine Derivatives Category chemicals are presented in Table 2. Robust Summaries for the reliable studies are provided in Appendix A. Robust Summaries for QSAR Estimates are provided in Appendix B. The Test Plan for Physical/Chemical Properties is outlined in Table 5. As described above, where possible, the physical/chemical property estimation program EPIWIN version 3.10 was used to derive estimates. In general, EPIWIN estimates must be interpreted with a great deal of professional judgment. However, the model estimates for the physical chemical properties of the Pyridine and Pyridine Derivatives Category chemicals are, in most cases, identical or very similar to the reliable measured data.

The QSAR estimates are based on structure and, therefore, can be made only for substances for which a structure can be defined. Thus, a complete set of model data was generated for the seven Pyridine and Pyridine Derivatives Category chemicals with defined structures. The available data for physical/chemical properties are summarized below:

Reliable data for melting and boiling points ranged from approximately –70 to 50°C and 106°C to 240°C, respectively. Melting points for most members of the category were less than 4°C with the exception of the two nitriles of pyridine (nicotinonitrile; CAS RN 100-54-9 and picolinonitrile; CAS RN 100-70-9), which had melting points of 50 and 29°C, respectively. Boiling points followed a similar trend, i.e. the members of the category could be grouped together with values ranging from 106 to 145°C, except for the two nitriles of pyridine (CAS RNs 100-54-9 and 100-70-9), which had higher boiling points of 240 and 222°C, respectively. EPIWIN predicted values that were very similar to the reliable data for chemicals in cases for which both types of values were available. Although measured data were not available and predictions could not be made for pyridine, alkyl derivs. (CAS RN 68391-11-7) or pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), because of their higher molecular weights and more complex structures they are expected to have melting points and boiling points at the higher ends of the ranges of –70 to 50°C and 106 to 240°C, respectively. The Work Group proposes to conduct studies to fulfill these endpoints for pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5).

Reliable data for vapor pressure values ranged from approximately 8 to 32 mm Hg and model predicted values were very similar in cases for which both values existed. Only predicted values were available for the two nitriles of pyridine (CAS RN 100-54-9 and 100-70-9). The predicted

values for the two nitriles of pyridine, which are solids at ambient temperature, were more than an order of magnitude lower than the members of the category with reliable data. Although measured data were not available and predictions could not be made for pyridine, alkyl derivs. (CAS RN 68391-11-7) or pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), because of their higher molecular weights and more complex structures they are expected to have vapor pressure values lower than the other members of the category that are liquids at ambient temperatures. The Work Group proposes to conduct studies to fulfill this endpoint for pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5).

Reliable data for octanol/water partition coefficient (log K_{ow}) ranged from approximately 0.6 to 2.6. Model-predicted values were similar in cases for which both values existed. Only model predictions for 3-picoline (CAS RN 108-99-6) and the two nitriles of pyridine (CAS RNs 100-54-9 and 100-70-9) were available (i.e. 1.35, 0.35 and 0.35, respectively), but the values were similar to the reliable data available for the other category members. The reliable and predicted octanol/water partition coefficient data clearly indicate that the Pyridine and Pyridine Derivative Category chemicals are not bioaccumulative. Although measured data were not available and predictions could not be made for pyridine, alkyl derivs. (CAS RN 68391-11-7) or pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), because of their expected high water solubility their log K_{ow} values are predicted to be within the same range (i.e. <2.6) as the other members of the category. The Work Group proposes to conduct studies to fulfill this endpoint for pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5).

Reliable data and model predictions for water solubility indicated that all of the Pyridine and Pyridine Derivative Category chemicals are highly soluble in water. Although measured data were not available and predictions could not be made for pyridine, alkyl derivs. (CAS RN 68391-11-7) or pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), because of their related structures to the other members of the Pyridine and Pyridine Derivative Category they are expected to be highly water soluble. Hawkins (1988) provides numerous examples of biotransformations of drugs and chemicals based on the pyridine ring structure. These drugs and chemicals have higher molecular weights and contain more complex functional groups than the members of the Pyridine and Pyridine Derivatives Category. These structures and biotransformation pathways indicate that even these higher molecular weight and more complex chemicals are metabolized and predominantly eliminated in urine. The Work Group proposes to conduct studies to fulfill this endpoint for pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5).

<u>Summary – Physical/Chemical Properties (Table 2)</u>
Adequate reliable data were available for six and seven of the nine chemicals for melting and boiling points, respectively. Four chemicals had reliable data for vapor pressure indicating that the liquid Pyridine and Pyridine Derivative Category chemicals are volatile. This property is

expected for organic solvents that have relatively low molecular weights and little substitution (see Text Table B). Model data indicates that the two nitrile substituted pyridine derivatives, which are solids at ambient temperatures, are not volatile. The Pyridine and Pyridine Derivative Category chemicals are highly water soluble and their low log K_{ow} values are low, consistent with their water solubility. The chemicals in the category would not be expected to bioaccumulate based on the K_{ow} measurements and/or predictions. Modeled data for physical/chemical properties, in most cases, were very similar to measured data. Therefore, modeled data for endpoints without reliable measured data are considered adequate with a high degree of confidence. The measured and modeled data and industrial experience with these chemicals support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals having closely-related structures, behave similarly or predictably from the perspective of physical/chemical properties.

Additional Data – Physical/Chemical Properties

The test plan for physical/chemical properties is summarized in Table 5. Melting point, boiling point, vapor pressure, octanol/water partition coefficient and water solubility data for the Pyridine and Pyridine Derivatives Category chemicals with defined structures are adequate for the program and no additional data development is suggested. The Work Group proposes to conduct melting point, boiling point, vapor pressure, octanol/water partition coefficient and water solubility studies to fulfill these endpoints for pyridine, alkyl derivs. (CAS RN 68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5). However, the properties for pyridine, alkyl derivs. (CAS RN 68391-11-7) are expected to be similar to the methyl derivatives of pyridine. Its CAS description indicates that pyridine, alkyl derivs. (CAS RN 68391-11-7) is "the complex combination of polyalkylated pyridines derived from coal tar distillation or as high-boiling distillates approximately above 150 °C (302 °F) from the reaction of ammonia with acetaldehyde, formaldehyde or paraformaldehyde." Also, one of the Work Group members provided the following additional information: "Pyridine, alkyl derivs. (CAS RN 68391-11-7) is a UVCB material with unspecified structure. A GC/MS analysis has shown a broad range of components including alkyl pyridines, lutidines, collidines, picolines and numerous non-characterized reaction products with no single substance or class dominating."

Environmental Fate and Ecotoxicity QSAR Estimates and Correlation to Reliable Data

The available reliable data and QSAR estimates for the environmental fate and effects of the Pyridine and Pyridine Derivatives Category chemicals are presented in Table 3. Robust Summaries for the reliable studies are provided in Appendix A and Robust Summaries for QSAR Estimates are provided in Appendix B.

Models for atmospheric photodegradation were used according to EPA guidelines. Modeling of the Pyridine and Pyridine Derivatives Category chemicals indicated that these chemicals would be expected to have varying degrees of degradation upon exposure to ambient light ($t_{1/2}$ values ranging from 0.121 to 163.72 days) with degradation times directly correlated with molecular weight and degree of substitution (see Text Table B). The Work Group does not expect that pyridine, alkyl derivs. (CAS RN 68391-11-7) or pyridinium, 1-(phenylmethyl)-, Et Me derivs.,

chlorides (CAS RN 68909-18-2) would fall outside of this predicted range of values for photodegradation.

The water stability of the Pyridine and Pyridine Derivatives Category chemicals could not be modeled since the structures of these chemicals did not meet the requirements of the EPIWIN submodel database. The model cannot calculate water stability for chemicals that do not meet the criteria of neutral organic compounds with structures that can be hydrolyzed. By deduction, this allows one to conclude that the Pyridine and Pyridine Derivatives Category chemicals are stable in water.

For those chemicals that could be modeled for environmental transport and distribution (Level III Mackay-type, fugacity-based models), distribution to air, water and soil was predicted with no appreciable distribution to sediment following their entry into the environment via air. Consistent with the vapor pressure data, the lower molecular weight, less substituted chemicals had higher predicted distribution to air (70% for piperidine CAS RN 110-89-4; 79% for pyridine CAS RN 110-86-1) with increasing proportion of distribution to water and soil (up to approximately 40% combined for methyl derivatives and up to approximately 97% combined for nitrile derivatives) as molecular weight and substitution increase. The Work Group does not expect that pyridine, alkyl derivs. (CAS RN 68391-11-7) would fall outside of the predicted range of values predicted for methyl derivatives of pyridine for environmental transport and distribution. On the other hand, pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) would be expected to distribute more to the soil compartment than methyl derivatives of pyridine (range 11 – 17%) because of the cationic nature of the molecule and, in this case, could behave more like the nitrile derivatives of pyridine rather than the pyridine or methyl or alkyl derivatives of pyridine.

Regarding biodegradation, measured data exist for six of the nine Pyridine and Pyridine Derivatives Category chemicals. The amount of biodegradation observed in the studies depended on the medium used in the experiment (water, soil, sludge or sediment), whether the tests were conducted in aerobic or anaerobic conditions, and the concentration of bacteria (contaminated vs. uncontaminated) in the media. In general, rapid and complete biodegradation was observed in those cases with adequate oxygenation and bacterial counts. On the other hand, anaerobic conditions tended to provide poor biodegradation even over extended periods (up to one year). Model predictions for biodegradation, made for piperidine (CAS RN 110-89-4) estimated short half-lives for water, soil and sediment. Pyridine, alkyl derivs. (CAS RN 68391-11-7) would be expected to biodegrade in a manner similar to methyl derivatives of pyridine, since it only differs from them slightly in the length of its alkyl chains. Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) would be expected to adsorb to the solid phase in biodegradation studies because of its cationic surfactant nature. However, in the environment it is not expected to be persistent in the water column, and microbial degradation would be expected to occur readily on to the solid phase in the environment. Details on purity of the test substance, culture conditions and the statistical analysis data were provided in robust summaries, when available. Forty-three biodegradation studies under various testing scenarios were reported for the nine members of the Pyridine and Pyridine Derivatives Category. To the Work Group this seems to be an extremely well studied endpoint. Although the results are variable depending on the experimental conditions employed in these studies, it can be

concluded confidently that rapid and complete biodegradation occurs in those cases with adequate oxygenation and bacterial counts (i.e., pyridine, 4-picoline, 3-picoline, 2-picoline, nicotinonitrile and picolinonitrile). However, anaerobic conditions tended to provide poor biodegradation even over extended periods (up to one year). The Work Group asserts that the U.S. EPA HPV goal of hazard identification has been adequately addressed and has no plans to conduct additional biodegradation testing for any of the chemicals in the Pyridine and Pyridine Derivatives Category.

ECOSAR estimates for acute fish, daphnid and algal toxicity were modeled for the seven chemicals with defined structures and, depending on the endpoint, reliable measured data were available for six (fish), three (invertebrates) or one (algae) chemicals. Reliable measured data for acute toxicity to fish were available for six of the chemicals with LC_{50} values ranging from 40 mg/l (pyridine, alkyl derivs. [CAS RN 68391-11-7]) to <1000 mg/l (3-picoline [CAS RN 108-99-6]). Measured and predicted LC_{50} values for Pyridine and Pyridine Derivatives Category chemicals generally fall between 100 and 1000 mg/l. Agreement between measured and predicted LC_{50} values, when available, is acceptable. Because of its cationic surfactant nature, pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) would be expected to be toxic to fish at relatively low concentrations similar to pyridine (CAS RN 110-86-1) and pyridine, alkyl derivs. (CAS RN 68391-11-7). Nitrile derivatives of pyridine are predicted to show relatively low toxicity to fish as the three methyl derivatives of pyridine have predicted LC_{50} values of 2745 mg/l, and picolinonitrile (CAS RN 100-70-9) has a reliable LC_{50} value of 726 mg/l.

Acute EC_{50} reliable measured values for daphnid ranged from 69 mg/l for pyridine, alkyl derivs. (CAS RN 68391-11-7) to 2470 mg/l for pyridine (CAS RN 110-86-1); although pyridine results with two other species of daphnid had EC_{50}s ranging from 575 to 1755 mg/l. With the exception of piperidine (CAS RN 110-89-4) and pyridine, alkyl derivs. (CAS RN 68391-11-7), measured and predicted EC_{50} values for Pyridine and Pyridine Derivatives Category chemicals are >100 mg/l. Agreement between measured and predicted LC_{50} values, when available, is acceptable. Because of its cationic surfactant nature, pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) would be expected to be toxic to invertebrates at relatively low concentrations similar to piperidine (CAS RN 110-89-4) and pyridine, alkyl derivs. (CAS RN 68391-11-7). Nitrile derivatives of pyridine are predicted to be nontoxic to invertebrates with LC_{50} values of >2600 mg/l.

An algae EC_{50} reliable measured value of 320 mg/l was available for 3-picoline (CAS RN 108-99-6) and agreement between its measured and predicted values is acceptable. Pyridine and methyl derivatives of pyridine are predicted to have algal EC_{50}s between 174 and 628 mg/l. Because of its cationic surfactant nature, pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2) would be expected to be toxic to algae at relatively low concentrations similar to piperidine (CAS RN 110-89-4). Nitrile derivatives of pyridine are predicted to be nontoxic to algae with EC_{50} values of 1492 mg/l.

Summary – Environmental Fate and Ecotoxicity (Table 3)

Only model estimates were available for photodegradation and fugacity of the Pyridine and Pyridine Derivatives Category chemicals. The other exclusively modeled value, stability in

water, could not be calculated for this group of chemicals. Atmospheric photodegradation was predicted to vary depending on molecular weight and substitution. Short half-lives were predicted for the lower molecular weight chemicals, piperidine (CAS RN 110-89-4), pyridine (CAS RN 110-86-1) and methyl pyridines, with substantially longer degradation rates for the two nitrile compounds (CAS RNs 100-54-9 and 100-70-9). However, the nitrile derivatives of pyridine were predicted by fugacity modeling to partition to soil and water to a much greater degree than to air. Based on the assumption that release of the chemicals to the environment is all via air, predicted distribution of the Pyridine and Pyridine Derivatives Category chemicals in the environment was to air, water and soil, with < 1% predicted to distribute to the sediment compartment. Biodegradation, given adequate oxygenation and bacteria counts, is rapid; however, anaerobic test conditions result in little degradation in most studies.

The atmospheric photodegradation estimates for the Pyridine and Pyridine Derivatives Category chemicals indicate that piperidine (CAS RN 110-89-4), which is the lower molecular weight, non-aromatic and unsubstituted chemical in the category, would be expected to degrade rapidly ($t_{1/2}$ < 1 day) when exposed to UV light in the atmosphere. Pyridine (CAS RN 110-86-1) and the three methyl derivatives of pyridine, which are the higher molecular weight, aromatic and substituted chemicals in the category, would be expected to photodegrade more slowly ($t_{1/2} \approx$ 30 or 10 days, respectively). The nitriles derivatives of pyridine are predicted to photodegrade even more slowly ($t_{1/2} \approx$ 164 days). However, the nitrile derivatives of pyridine were predicted by fugacity modeling to partition to air much less favorably than to soil and water.

The water stability of Pyridine and Pyridine Derivatives Category chemicals could not be modeled since their structures did not meet the requirements of the EPIWIN submodel's database. Regarding stability in water, in the guidance document entitled, "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program," the following is stated:

> "Hydrolysis is the reaction of a substance with water in which the water molecule or the hydroxide ion displaces an atom or group of atoms in the substance. Chemical hydrolysis at a pH normally found in the environment (i.e., pH 5 to 9) can be important for a variety of chemicals that have functional groups that are potentially hydrolysable, such as alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters."

The Pyridine and Pyridine Derivatives Category chemicals do not contain the listed functional groups and, because of this fact, hydrolysis in the environment is not predicted to occur.

The fugacity model (Level III) results for transport and distribution predict that the lower molecular weight, unsubstituted chemicals distribute substantially to the air with lesser amounts in water and soil. As molecular weight and substitution increase in the category, greater distribution to water and soil and less to air is predicted. This trend is consistent with the vapor pressure data.

There are adequate measured data across the Pyridine and Pyridine Derivatives Category to allow the conclusion that these chemicals are biodegradable in the presence of adequate oxygen and bacteria; however, they are relatively stable under anaerobic and/or sterile environments**.**

Measured values for acute aquatic toxicity indicate that the Pyridine and Pyridine Derivatives Category chemicals are slightly to moderately toxic to fish, invertebrates and algae. Modeled data for acute aquatic toxicity were generally consistent with the reliable measured values in cases for which both existed, but the accuracy of modeled data for some of the Pyridine and Pyridine Derivatives Category chemicals could not be confirmed. The measured and modeled data support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals having closely-related structures, behave similarly or predictably from the perspective of environmental fate and ecotoxicity. Differences between the reliable acute fish LC_{50}s for the Pyridine and Pyridine Derivatives Category chemicals range from 40 mg/l (pyridine, alkyl derivs.; CAS RN 68391-11-7) to <1000 (3-picoline; CAS RN 108-99-6), i.e. a factor of only 25-fold, or less than an order of magnitude.

Additional Data – Environmental Fate and Ecotoxicity
The environmental fate and ecotoxicity test plan is summarized in Table 6. Modeling estimates for photodegradation and environmental distribution for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is suggested. Biodegradation data for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is suggested. Acute fish, daphnid and algae data and/or ECOSAR model estimates for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is suggested.

Human Health-Related Reliable Data

The human health-related data for SIDS endpoints for the nine Pyridine and Pyridine Derivatives Category chemicals are presented in Table 4. Robust Summaries for the reliable studies are provided in Appendix A.

Acute toxicity data were available across the Pyridine and Pyridine Derivatives Category. Rat oral LD_{50} values ranged from 337 mg/kg for piperidine (CAS RN 110-89-4) to 1475 mg/kg (in males) for nicotinonitrile (CAS RN 100-54-9). Although acute rat oral toxicity studies were identified in literature searches for pyridine (CAS RN 110-86-1), none of these reports could be scored as reliable according to the Klimisch *et al.* (1997) criteria employed for this assessment. However, the rat oral LD_{50} values found for pyridine in the literature ranged from 800 to 1600 mg/kg, which are in good agreement with the rat oral LD_{50} values for the other chemicals of the Pyridine and Pyridine Derivatives Category. LC_{50} values from acute inhalation toxicity studies were between >1000 ppm for 4-picoline (CAS RN 108-89-4) and >4900 and <6000 ppm for pyridine (CAS RN 110-86-1). Rabbit acute dermal toxicity LD_{50} values ranged from approximately 200 mg/kg for 3-picoline and 2-picoline (CAS RNs 108-99-6 and 109-06-8, respectively) to approximately 2000 mg/kg for pyridine and nicotinonitrile (CAS RNs 110-86-1 and 100-54-9). These data indicate that piperidine (CAS RN 110-89-4), pyridine, methyl and alkyl derivatives of pyridine, nicotinonitrile and picolinonitrile are slightly to moderately toxic following acute exposures.

A four-month inhalation study was conducted with piperidine (CAS RN 110-89-4) using rats and rabbits at exposure concentrations of 0.01 and 0.002 mg/l. The results showed that prolonged exposure to piperidine at concentrations of 0.01 mg/l caused body weight, nervous system, cardiovascular, liver, kidney and spermatogenesis effects; whereas, morphological changes of organs for animals exposed to 0.002 mg/l piperidine were much less prominent than those of the higher exposure group and were fully reversible. In a 50-week drinking water study in Sprague-Dawley rats, the incidence of tumors for rats chronically exposed to 0.09% piperidine (CAS RN 110-89-4) or 0.09% piperidine with 0.2% sodium nitrite was not significantly increased as compared to control rats receiving 0.2% sodium nitrite in drinking water. Numerous repeated dose oral toxicity studies, including subchronic and chronic studies in mice and three strains of rats were available for pyridine (CAS RN 110-86-1). Oral NOAELs for pyridine ranged from 1 to 15 mg/kg/day with hepatic toxicity as the primary determinant of the effect doses. In addition to the oral repeated dose toxicity studies, a 4-day inhalation study was conducted with pyridine in rats to evaluate its effects on the nasal epithelium. Olfactory epithelial lesions were observed at both 5 and 444 ppm. In another inhalation toxicity study, following 10 exposures to a single concentration (290 ppm) of 3-picoline (3-methylpyridine; CAS RN 108-99-6), increased liver weights were observed in male rats (only sex tested). Also, no effects were observed in rats exposed to 5, 35 or 100 ppm of 2-picoline (2-methylpyridine; CAS RN 109-06-8) for 6 hours/day, 5 days/week for 6 months, although only limited tissues were examined histopathologically. A 28-day oral gavage study in rats was conducted with nicotinonitrile (CAS RN 100-54-9) with the critical endpoint being liver toxicity at 30 mg/kg/day and a NOAEL was identified as 5 mg/kg/day. Repeated dose toxicity studies were not available for the other chemicals in the Pyridine and Pyridine Derivatives Category.

A number of *in vitro* genetic toxicity studies including the *S. typhimurium/E. coli* reverse mutation (Ames), mouse lymphoma cell mutagenicity, DNA unwinding, chromosomal aberration, sister chromatid exchange, HGPRT mutagenicity, and/or DNA single strand break assays were available for piperidine (CAS RN 110-89-4) and pyridine (CAS RN 110-86-1) and its methyl derivatives. Almost all of these assays indicated these chemicals are neither mutagenic nor clastogenic. Exceptions included a positive response of piperidine in the mouse lymphoma cell mutagenicity assay and a positive response for pyridine in one of nine Ames assays (positive assay conducted in a single, unusual strain of *Salmonella*). When interpreting the results of *in vitro* mammalian cell assays performed before 1986, in particular the mouse lymphoma forward mutation assay, it is important to recognize that the investigators usually did not properly control pH and ionic strength of the test media. Mammalian cells *in situ* rely on complex regulatory mechanisms to maintain homeostatic conditions and those in culture are not equipped to respond to environmental changes; therefore, it is essential that culture media used to support *in vitro* mammalian cell assays be maintained at a pH of approximately 6.8 to 7.5. Reduced pH of test media or changes in culture osmolality due to air-oxidizable test agents may cause false positive results in mammalian cell assays, especially those that employ S9 metabolic activation systems. Studies have shown that increased acidity facilitates the breakdown of S9 components into mutagenic agents (Brusick, 1986; Caldwell, 1993). A bacterial mutation assay using four strains of *Salmonella* and a strain of *E. coli* and a chromosomal aberration assay using CHL/IU cells were conducted with nicotinonitrile (CAS RN 100-54-9); both assays were negative. The weight-of-evidence suggests that Pyridine and Pyridine Derivatives Category

chemicals are not mutagenic. This conclusion is supported by a number of *in vivo* mutagenicity assays and carcinogenicity studies with negative results for pyridine (CAS RN 110-86-1) (Table 4).

For the Pyridine and Pyridine Derivatives Category chemicals, evaluation of potential for reproductive effects is satisfied by evaluation of spermatogenesis and histological evaluation of reproductive organs from repeated dose toxicity studies. Reproductive organs were examined and spermatogenesis evaluated for piperidine (CAS RN 110-89-4) in a four-month inhalation study conducted with rats and rabbits, and reproductive organs were examined in a 50-week drinking water study with Sprague-Dawley rats. Spermatogenesis was reported as being adversely affected in the four-month inhalation study. Six of the repeated dose toxicity studies with pyridine (CAS RN 110-86-1) meet the requirements of screening for reproductive effects by histological evaluation of reproductive organs. Also, sperm motility in exposed male mice was significantly decreased relative to controls in a 13-week drinking water study with pyridine; however, sperm motility and vaginal cytology were unaffected in rats exposed to pyridine during a 13-week drinking water study. Necrosis of spermatocytes and spermatids, and vacuolation of Sertoli cells were noted in male Sprague-Dawley rats dosed by oral gavage to nicotinonitrile (CAS RN 100-54-9) for 28-days. No other data were available for reproductive toxicity screening of the Pyridine and Pyridine Derivatives Category chemicals.

Piperidine (CAS RN 110-89-4) was evaluated for developmental toxicity potential in an inhalation study with female rats that were exposed during the entire period of gestation, on gestation day 4 or on gestation day 9 to 3, 15 or 100 mg piperidine/m^3. In studying the embryotropic effect of piperidine the most significant changes occurred when the animals were exposed to 100 mg/m^3 during the entire course of pregnancy and on the fourth day of pregnancy. Piperidine had no specific embryotropic effect and it is not a selective developmental toxicant. No other developmental toxicity studies were available for the Pyridine and Pyridine Derivatives Category chemicals.

Summary – Human Health-Related Data (Table 4)

Adequate acute oral LD_{50} studies were available throughout the category indicating most of the chemicals are of moderate acute toxicity. A four-month inhalation study with piperidine (CAS RN 110-89-4) indicates it may have nervous system, cardiovascular, liver, kidney and spermatogenesis effects, but a 50-week drinking water study in rats demonstrated that it is not tumorigenic. Several repeated dose toxicity studies for pyridine (CAS RN 110-86-1) indicate it is moderately toxic, due to its effects on the liver, and is not carcinogenic. IARC (WHO, 2000) determined that evidence for cancer in humans was inadequate and evidence for carcinogenicity in experimental animals was limited. Therefore, pyridine was considered by IARC as *not classifiable as to carcinogenicity to humans* (Group 3). Repeated inhalation exposure to 290 ppm of 3-picoline (CAS RN 108-99-6) caused elevated liver weights after 10 exposures; however, this change was reversible after a 13 day recovery period. 2-Picoline (CAS RN 109-06-8) was administered via inhalation at concentrations as high as 100 ppm for six months to rats and there were no signs of toxicity or deficits in motor function performance, no changes in body or organ weights, no differences between hematological parameters, no gross lesions at necropsy, and histopathologic examination did not reveal any treatment-related effects. A 28-day oral repeated dose toxicity study for nicotinonitrile (CAS RN 100-54-9) indicates that it

is moderately toxic and causes liver toxicity at 5 mg/kg/day. The weight-of-evidence from *in vitro* studies indicates that Pyridine and Pyridine Derivatives Category chemicals are not mutagenic. Reproductive screening evaluations using several repeated dose toxicity studies indicates that piperidine (CAS RN 110-89-4), pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN 100-54-9) may be male reproductive toxicants. Piperidine had no specific embryotropic effect and it was not a selective developmental toxicant when female rats were exposed during the entire period of gestation, on gestation day 4 or on gestation day 9 to 3, 15 or 100 mg piperidine/m^3. The available data support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals possess similar human health-related data.

Additional Data – Human Health-Related Data

The human health-related test plan is summarized in Table 7. The Work Group proposes to provide additional developmental toxicity data and to improve the information on reproductive toxicity for pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN 100-54-9) by conducting studies according to OECD 421 testing guidelines (reproduction/developmental toxicity screening test). The Work Group asserts that testing pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN
100-54-9) using the OECD 421 testing guideline also fulfills SIDS data needs for two endpoints (reproduction and developmental toxicity) for the closely-related methyl, alkyl and nitrile derivatives of pyridine that are members of the Pyridine and Pyridine Derivatives Category.

Justification for a Pyridine and Pyridine Derivatives Category – Physical/Chemical Properties Data, Environmental Fate and Ecotoxicity Data, and Human Health-Related Data

Adequate reliable data were available for six and seven of the nine chemicals for melting and boiling points, respectively. Four chemicals had reliable data for vapor pressure indicating that the liquid Pyridine and Pyridine Derivative Category chemicals are volatile. This property is expected for organic solvents that have relatively low molecular weights and little substitution. Model data indicate that the two nitrile substituted pyridine derivatives, which are solids at ambient temperatures, are not volatile. The Pyridine and Pyridine Derivative Category chemicals are highly water soluble and their low log K_{ow} values are low, consistent with their water solubility. The chemicals in the category would not be expected to bioaccumulate based on the K_{ow} measurements and/or predictions. Modeled data for physical/chemical properties, in most cases, were very similar to measured data. Therefore, modeled data for endpoints without reliable measured data are considered adequate with a high degree of confidence. The measured and modeled data and industrial experience with these chemicals support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals having closely-related structures, behave similarly or predictably from the perspective of physical/chemical properties.

Only model estimates were available for photodegradation and fugacity of the Pyridine and Pyridine Derivatives Category chemicals. The other exclusively modeled value, stability in water, could not be calculated for this group of chemicals since their structures did not meet the requirements of the HYDROWIN submodel's database. Atmospheric photodegradation was predicted to vary depending on molecular weight and substitution. Short half-lives were predicted for the lower molecular weight chemicals, piperidine (CAS RN 110-89-4), pyridine

(CAS RN 110-86-1) and methyl pyridines, with substantially longer degradation rates for the two nitrile compounds (CAS RNs 100-54-9 and 100-70-9). However, the nitrile derivatives of pyridine were predicted by fugacity modeling to partition to soil and water to a much greater degree than to air. Based on the assumption that release of the chemicals to the environment is all via air, predicted distribution of the Pyridine and Pyridine Derivatives Category chemicals in the environment was to air, water and soil, with < 1% predicted to distribute to the sediment compartment. There are adequate measured data across the Pyridine and Pyridine Derivatives Category to allow the conclusion that these chemicals are biodegradable in the presence of adequate oxygen and bacteria; however, they are relatively stable under anaerobic and/or sterile environments.

Measured values for acute aquatic toxicity indicate that the Pyridine and Pyridine Derivatives Category chemicals are slightly to moderately toxic to fish, invertebrates and algae. Modeled data for acute aquatic toxicity were generally consistent with the reliable measured values in cases for which both existed, but the accuracy of modeled data for some of the Pyridine and Pyridine Derivatives Category chemicals could not be confirmed. The measured and modeled data support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals having closely-related structures, behave similarly or predictably from the perspective of environmental fate and ecotoxicity. Differences between the reliable acute fish LC_{50}s for the Pyridine and Pyridine Derivatives Category chemicals range from 40 mg/l (pyridine, alkyl derivs.; CAS RN 68391-11-7) to <1,000 (3-picoline; CAS RN 108-99-6), i.e. a factor of only 25-fold.

Adequate acute oral LD_{50} studies were available throughout the category indicating most of the chemicals are of moderate acute toxicity. A four-month inhalation study with piperidine (CAS RN 110-89-4) indicates it may have nervous system, cardiovascular, liver, kidney and spermatogenesis effects, but a 50-week drinking water study in rats demonstrated that it is not tumorigenic. Several repeated dose toxicity studies for pyridine (CAS RN 110-86-1) indicate it is moderately toxic, due to its effects on the liver, and is not carcinogenic. Repeated inhalation exposure to 290 ppm of 3-picoline (CAS RN 108-99-6) caused elevated liver weights after 10 exposures; however, this change was reversible after a 13-day recovery period. 2-Picoline (CAS RN 109-06-8) was administered via inhalation at concentrations as high as 100 ppm for six months to rats and there were no signs of toxicity or deficits in motor function performance, no changes in body or organ weights, no differences between hematological parameters, no gross lesions at necropsy, and histopathologic examination did not reveal any treatment-related effects. A 28-day oral repeated dose toxicity study for nicotinonitrile (CAS RN 100-54-9) indicates that it is moderately toxic and causes liver toxicity at 5 mg/kg/day. The weight-of-evidence from *in vitro* studies indicates that Pyridine and Pyridine Derivatives Category chemicals are not mutagenic. Reproductive screening evaluations using several repeated dose toxicity studies indicate that piperidine (CAS RN 110-89-4), pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN 100-54-9) may be male reproductive toxicants. Piperidine had no specific embryotropic effect and it was not a selective developmental toxicant when female rats that were exposed during the entire period of gestation, on gestation day 4 or on gestation day 9 to 3, 15 or 100 mg piperidine/m^3. The available data support the conclusion that the Pyridine and Pyridine Derivatives Category chemicals possess similar human health-related data, and in particular, target organs appear to be the liver and the male reproductive tract.

Using the guidance provided by EPA in its "Letters to Manufacturers/Importers" (EPA OPPT, 1999), the Work Group developed its Test Plan to appropriately "…maximize the use of existing and scientifically adequate data to minimize further testing…" and "…maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships."

Summary of Test Plan

The test plan for physical/chemical properties is summarized in Table 5. The Work Group proposes to conduct melting point, boiling point, vapor pressure, octanol/water partition coefficient and water solubility studies to fulfill these endpoints for pyridine, alkyl derivs. (CAS RN
68391-11-7) and pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (CAS RN 68909-18-2), in order to strengthen the rationale for their membership in the Pyridine and Pyridine Derivatives Category (see Table 5).

The environmental fate and ecotoxicity test plan is summarized in Table 6. Modeling estimates for photodegradation and environmental distribution for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is proposed. Biodegradation data for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is suggested. Acute fish, daphnid and algae data and/or ECOSAR model estimates for the Pyridine and Pyridine Derivatives Category chemicals are adequate and no additional data development is suggested.

The human health-related test plan is summarized in Table 7. The Work Group proposes to provide additional developmental toxicity data and to improve the information on reproductive toxicity for pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN 100-54-9) by conducting studies according to OECD 421 testing guidelines (reproduction/developmental toxicity screening test). The Work Group asserts that testing pyridine (CAS RN 110-86-1) and nicotinonitrile (CAS RN
100-54-9) using the OECD 421 testing guideline also fulfills SIDS data needs for two endpoints (reproduction and developmental toxicity) for the closely-related methyl, alkyl and nitrile derivatives of pyridine that are members of the Pyridine and Pyridine Derivatives Category.

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Table 1
Structures of the Pyridine and Pyridine Derivatives Category Chemicals

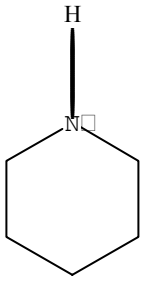
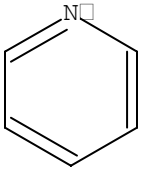
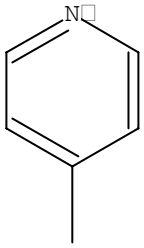
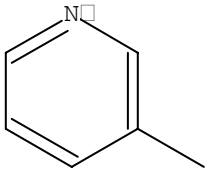
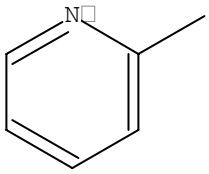
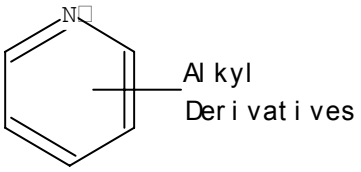
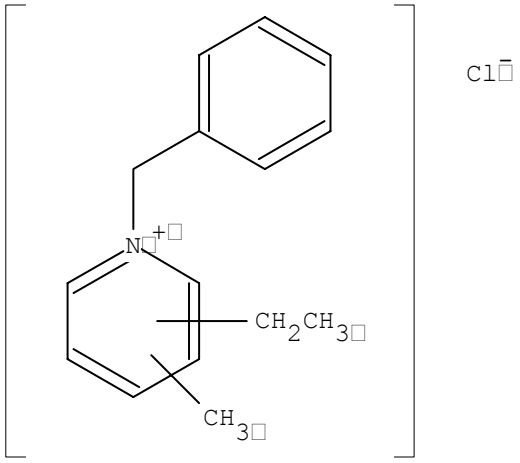
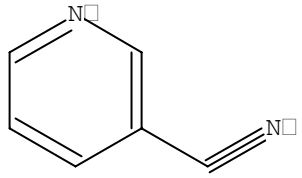
 Piperidine 110-89-4	 Pyridine 110-86-1
 4-Picoline 108-89-4	 3-Picoline 108-99-6
 2-Picoline 109-06-8	 Pyridine, alkyl derivs. 68391-11-7

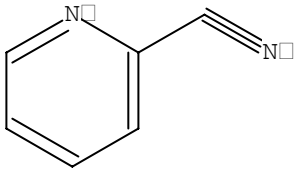
Table 1 (continued)
Structures of the Pyridine and Pyridine Derivatives Category Chemicals



Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides
68909-18-2



Nicotinonitrile
100-54-9



Picolinonitrile
100-70-9

Table 2

Physical/Chemical Properties Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure[a] (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility[a] (mg/l)
Piperidine 110-89-4	-24.69 -11.03	**106.3** 127.9 106.2	**32.1** 28.5 32.1	**0.84** 1.19	**1 x 10^6** 249,400 1 x 10^6
Pyridine 110-86-1	**-41.6** -44.54 -41.6	**115.2** 113.36 115.2	**20** 19.3 20.8	**0.64** 0.80	**Miscible** 936,300 1 x 10^6
4-Picoline 108-89-4	**3.66** **3.6** -25.92 3.66	**145** **145** **144.9** 136.41 145.3	**7.99** 5.05 5.77	**1.22** 1.35	**Soluble** **Infinite Solubility** **Miscible** 276,400 1 x 10^6
3-Picoline 108-99-6	**-18.3** -25.92 -18.1	**143 – 144** **143.9** 136.41 144.1	5.32 6.05	 1.35	**Miscible** **Miscible** 288,800 1 x 10^6
2-Picoline 109-06-8	**-70** **-66.8** -25.92 -66.7	**128 – 129** **128.8** 136.41 129.3	**10** **12.6** 10.6 11.2	**1.11** **2.58** [b] 1.35	**Freely Soluble** **Very soluble** 352,400 1 x 10^6
Pyridine, alkyl derivs. 68391-11-7	NC	NC	NC	NC	NC
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides 68909-18-2	NC	NC	NC	NC	NC

Table 2 (continued)

Physical/Chemical Properties Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure[a] (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility[a] (mg/l)
Nicotinonitrile 100-54-9	**50** 25.39 51	**240** 200.84 206.9	0.0262	0.35	**Soluble** 27,920
Picolinonitrile 100-70-9	**29** 25.39 29	**222** 200.84 224.5	0.102	0.35	**Soluble** 35,710

Note: Bold print indicates reliable empirical data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models and/or identified by models as a match in the U.S. EPA's Experimental Database. Robust Summaries are provided in Appendix B.
NC = Not calculable because these chemicals are UVCB.

[a] Values are at 25 °C unless otherwise noted.
[b] Value from regression equation for calculation of K_{ow} (see robust summary in Appendix A).

Table 3

Environmental Fate and Ecotoxicity Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish LC_{50} (mg/l)	Acute Toxicity to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)
Piperidine 110-89-4	k_{phot} = 8.86 E-11 $t_{½}$ = 0.121 d	NC	air: 70% water: 16% soil: 14% sediment: < 0.1%	$t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 15 d	130	8.2	10.4
Pyridine 110-86-1	k_{phot} = 3.70 E-11 $t_{½}$ = 28.9 d	NC	air: 79% water: 15% soil: 6% sediment: < 0.1%	**1) Soil 54% degraded at 16 d [a]** **2) Water = 97% degraded in 28 d [b]** **3) Soil, aerobic = 100% degraded in > 66 d and < 170 d** **Soil, anaerobic = 100% degraded in > 32 d and < 66 d** **4) Water = 94% degraded in 8 d [c]** **5) Soil = 63% degraded in 7 d** **6) Sludge, anaerobic = 58% degraded in 60 d** **7) River water = 100% degraded in 10 d [d]**	**99** 1113	**1165 [e]** **1755** **1130** **575** **2470** 1086	628

Please see footnotes on page 32.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish LC_{50} (mg/l)	Acute Toxicity to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)
4-Picoline 108-89-4	k_{phot} = 1.10 E-12 $t_{½}$ = 9.707 d	NC	air: 60% water: 23% soil: 17% sediment: < 0.1%	**1) Sediment, anaerobic = 0% degraded in 200 d** **2) Soil, aerobic = 68% degraded in 24 d [a]** **3) Water = 90% degraded in 14 d** **4) Soil, aerobic = 100% degraded > 66 d and < 170 d** **Soil, anaerobic = 100% degraded > 32 d and < 66 d** **5) Soil = 10 – 100% degraded in 90 d [f]** **6) Soil, anaerobic = 100% degraded in 45 d** **7) Sewage = 30 – 100% degraded in 7 d [g]** **8) Soil 69.2% degraded in 32 d [a]** **9) Soil, anaerobic = 35% or 90% degraded in 8 months [h]**	**400** 373	379	227

Please see footnotes on page 32.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish LC_{50} (mg/l)	Acute Toxicity to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)
3-Picoline 108-99-6	k_{phot} = 1.10 E-12 $t_{½}$ = 9.707 d	NC	air: 64% water: 22% soil: 14% sediment: < 0.1%	**1) Soil = 100% degraded in < 13 d** **2) Soil, aerobic < 1% degraded in 30 d [a]** **3) Water = 100% degraded in 14 d** **4) Soil = 0 – 100% degraded 90 d [f]** **5) Soil, anaerobic = 100% degraded in 30 d** **6) Activated sludge = 93.8% in 13 d [g]** **7) Sewage = 47 – 100% degraded in 7 d [i]** **8) Sediment, anaerobic = 0% degraded in 200 d** **9) Water = 96% degraded in 2 d** **10) Soil, anaerobic = 25% or 0% degraded in 8 months [h]** **11) Soil 69.3% degraded in 32 d [a]** **12) Activated sludge = 85% degraded in 29 d [c]** **13) Activated sludge, aerobic = 85% degraded in 28 d [c]**	**> 560 and <1000** 282	**320** 289	**320** 174

Please see footnotes on page 32.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish LC_{50} (mg/l)	Acute Toxicity to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)
2-Picoline 109-06-8	k_{phot} = 1.10 E-12 $t_{½}$ = 9.707 d	NC	air: 67% water: 22% soil: 11% sediment: < 0.1%	**1) Soil = 100% degraded < 13 d** **2) Sewage > 94% degraded in 7 d** **3) Soil, aerobic = 100% degraded > 14 d and < 33 d Soil, anaerobic = 100% degraded > 97 d** **4) Soil ≈ 49.3% degraded in 16 d** [a] **5) Soil = 0 – 100% degraded in 90 d** [f] **6) Soil, anaerobic = 92% or 0% degraded in 8 months** [h] **7) Water = 100% degraded in 14 d** **8) Sediment, anaerobic = 0% degraded in 200 d** **9) Water = 96% degraded in 2 d** **10) Soil = 56% degraded in 24 d** [a]	**897** 474	478	284

Please see footnotes on page 32.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish LC_{50} (mg/l)	Acute Toxicity to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)
Pyridine, alkyl derivs. 68391-11-7	NC	NC	NC	NC	**40** NC	**68.8** NC	NC
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides 68909-18-2	NC	NC	NC	NC	NC	NC	NC
Nicotinonitrile 100-54-9	k_{phot} = 6.53 E-14 $t_{½}$ = 163.72 d	NC	air: 11% water: 33% soil: 56% sediment: < 0.1%	**1) Sediment, anaerobic = 100% transformation to an intermediate in 23 d [j] 2) Sewage > 91% degraded in 7 d**	2745	2624	1492
Picolinonitrile 100-70-9	k_{phot} = 6.53 E-14 $t_{½}$ = 163.72 d	NC	air: 3% water: 34% soil: 63% sediment: < 0.1%	**1) Sewage = 20 – 61% degraded in 7 d [f] 2) Sediment, anaerobic = 100% transformation to an intermediate in 59 d [k]**	**726** 2745	2624	1492

Please see footnotes on page 32.

Table 3 (continued)

Note: Bold print indicates reliable empirical data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models and/or identified by models as a match in the U.S. EPA's Experimental Database. Robust Summaries are provided in Appendix B.
NC = Not calculable with the EPIWIN model.

[a] Reported value is based on portion of degradation attributed to release of inorganic nitrogen in test solutions.
[b] Several procedures (301A, 301B, 301C, 301D, 302B, 303A, AFNOR) reported in two studies; value reported is for 301B (as DOC removal) over 28 days.
[c] Reported value is based the measurements of carbon dioxide (CO_2) evolution.
[d] River die-away study; value for 0.2-20 mg/l. Higher concentrations degraded more slowly in a concentration-related manner.
[e] Three species of daphnia tested, one of which was tested in three different labs; all LC_{50} values are presented.
[f] Study examined aerobic and anaerobic degradation; lowest degradation in "unpolluted" anaerobic conditions, highest degradation in "polluted" aerobic conditions.
[g] Biodegradability was measured in a pilot treatment plant.
[h] Study conducted using "aquifer solids and water from a site adjacent to a landfill"; first degradation value under "sulfate-reducing conditions"; second degradation value under "methanogenic conditions."
[i] Degradation depended on acclimation period; first inoculum (unacclimated) had lowest degradation rate.
[j] The reported pseudo-first-order rate constant was 9.41 day^{-1} indicating a biodegradation half-life of < 1 day.
[k] The reported pseudo-first-order rate constant was 1.01 day^{-1} indicating a biodegradation half-life of < 1 day.

Table 4

Human Health-Related Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Acute Oral Toxicity LD_{50} (mg/kg)	Acute Inhalation Toxicity LC_{50} (ppm)	Acute Dermal Toxicity LD_{50} (mg/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity *In vitro*	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)	Additional Studies
Piperidine 110-89-4	**337** **633/536 (M/F)** **740** **405/488 (M/F)**	**> 2000 (0/6 died in 4 hrs)**	**0.32 ml/kg**	**0.002 mg/l[a]** **0.09% [b]**	**Negative (BMA) [c]** **Positive (ML) [d]**	**0.002 mg/l[a]** **0.09% [b]**	**3 mg/m^3 [e]**	
Pyridine 110-86-1	800 to 1600	**9010 (M)** **9020 (F) [f]** **> 4900 and < 6000** **< 4000 (5/6 died in within 14 days)**	**> 1000 and < 2000**	**1) 1.0 [g]** **2) LOAEL = 25 [h]** **3) 10 [i]** **4) 15 (F);** **LOAEL = 35 (M) [j]** **5) LOAEL = 12.5 [k]** **6) 10 [l]** **7) 7 [m]** **8) 10 [n]** **9) LOAEL = 8 [o]** **10) LOAEL = 5 ppm [p]**	**Negative /Positive (Ames) [q]** **Negative (Chrom. Aberration)[r]** **Negative (SCE) [r, s]** **Negative (SSB) [r, t]**	**> 50 [g]** **< 50 [i] (M)** **> 190 [i] (F)** **> 90 [l]** **> 33 [m]** **> 100 [n]** **> 36 [o]**		**1) Negative (*in vivo* Chrom. Aberration)** **2) Negative (*in vivo* MMT) [u]** **3) Negative (*in vivo* UDS) [v]** **4) Negative (*in vivo* SLRL) [r, w]** **5) Hepatotoxic (1.25 mmol/kg i.p. dose; 5 d)** **6) Olfactory lesions (5 or 444 ppm, inhalation; 6 hrs/d for 4 d)** **7) Not carcinogenic (3 to 100 mg/kg s.c. dose; 2x/wk for 52 wks)**

Please see footnotes on page 35.

Table 4 (continued)

Human Health-Related Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Acute Oral Toxicity LD_{50} (mg/kg)	Acute Inhalation Toxicity LC_{50} (ppm)	Acute Dermal Toxicity LD_{50} (mg/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity *In vitro*	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)	Additional Studies
4-Picoline 108-89-4	**841** **700** **700**	**< 9.17 g/m^3 (6/6 died in 5 hrs)** **< 17.5 g/m^3 (6/6 died in 2.5 hrs)** **> 1000 (1/6 died in 4 hrs)**	**> 200 and < 316** [x] **> 126 and < 200** [x] **0.27 ml/kg**		**Negative (Ames)** [r] **Negative (HGPRT)** **Negative (SSB)** [t]			
3-Picoline 108-99-6	**710** **630**	**< 11.82 g/m^3 (6/6 died in 5 hrs)** **> 1300 and < 3300**	**> 200 and < 1000** **> 126 and < 200** [x] **> 800 and < 2000**	**LOAEL = 290 ppm** [y]	**Negative (Ames)** [r] **Negative (HGPRT)** **Negative (SSB)** [t]			
2-Picoline 109-06-8	**> 950** **810**	**< 13.2 g/m^3 (6/6 died in 4 hrs)** **> 2000 and < 4000**	**> 252 and < 500** **> 200 and < 316** [x] **0.41 ml/kg**	**≥ 100 ppm** [z]	**Negative (Ames)** [r] **Negative (HGPRT)** **Negative (SSB)** [t]			
Pyridine, alkyl derivs. 68391-11-7	**2500** [aa]		**> 2 ml/kg**					
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides 68909-18-2	**50** [bb]							

Please see footnotes on page 35.

Table 4 (continued)

Human Health-Related Data for the Pyridine and Pyridine Derivatives Category

Chemical Name CAS RN	Acute Oral Toxicity LD_{50} (mg/kg)	Acute Inhalation Toxicity LC_{50} (ppm)	Acute Dermal Toxicity LD_{50} (mg/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity *In vitro*	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)	Additional Studies
Nicotinonitrile 100-54-9	**1100** **1475 (M)** **1455 (F)**		**> 2000 and < 4000**	**5** [cc]	**Negative (Ames)** **Negative (Chrom. Aberration)**	**30** [cc]		
Picolinonitrile 100-70-9	**500 mg (0/2 died)** **1000 mg (2/3 died)**							

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from reports that do not meet Klimisch *et al.* (1997) criteria for reliability; no Robust Summary is provided.
Empty block denotes data either are not available or are available and judged inadequate.
M – Males; F – Females

[a] 4-month inhalation study in rats and rabbits at 0.01 or 0.002 mg/l; adequate for SIDS/HPV reproductive screening.
[b] 50-week drinking water study in Sprague-Dawley rats at a concentration of 0.09%; adequate for SIDS/HPV reproductive screening.
[c] BMA – Bacterial mutagenicity assays; although the three studies did not comply fully with guidelines (e.g. fewer tester strains, fewer concentrations), this series of assays in combination indicate the test substance is negative with and without metabolic activation.
[d] ML – Mouse Lymphoma assay; positive in two assays without activation only; also, negative in DNA unwinding assay without activation (equivocal with activation).
[e] Inhalation study in rats exposed throughout pregnancy, on gestation day 4 or gestation day 9 to exposure concentrations of 3, 15 or 100 mg/m^3.
[f] 1-hour static exposure.
[g] 1.0 mg/kg/day for 90-day gavage study in Sprague-Dawley rats; adequate for SIDS/HPV reproductive screening.
[h] 13-week gavage study in mice.
[i] 13-week drinking water study in mice; adequate for SIDS/HPV reproductive screening.
[j] Chronic (2 year) drinking water study in mice.
[k] 13-week gavage study in Fischer 344/N rats.
[l] 13-week drinking water study in Fischer 344/N rats; adequate for SIDS/HPV reproductive screening.
[m] Chronic (2-year) drinking water in Fischer 344/N rats; adequate for SIDS/HPV reproductive screening.
[n] 13-week drinking water study in Wistar rats; adequate for SIDS/HPV reproductive screening.
[o] 2-year chronic drinking water study in Wistar rats; adequate for SIDS/HPV reproductive screening.
[p] 4-day inhalation study in rats; no NOAEL established.

Table 4 (continued)

[q] Negative in eight separate reverse mutation (Ames) assays; positive in a single strain *S. typhimurium* (TM677) with metabolic activation in a separate Ames test; also negative in two "forward mutation assay" and an "N-oxide syntheses" assay.

[r] This value was observed in multiple studies for which separate Robust Summaries have been provided in Appendix A.

[s] SCE – Sister chromatid exchange assay.

[t] SSB – DNA single strand break assay.

[u] MMT – Mouse micronucleus test.

[v] UDS – Unscheduled DNA synthesis test.

[w] SLRL – Sex-linked recessive lethal mutation.

[x] Minimal lethal dose (study conducted with 1 animal/dose) – classified as "highly toxic by skin absorption".

[y] 2-week inhalation study in male (only) rats – single exposure concentration used (290 ppm) – increased liver weight observed.

[z] 6-month inhalation study in Sprague-Dawley rats.

[aa] Mixture of pyridine, HCl, methanol, surfactant, water.

[bb] Mixture of pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides; surfactant; isopropanol; water; thiourea.

[cc] 28-day oral gavage study in Sprague-Dawley rats; adequate for SIDS/HPV reproductive screening.

Table 5
Proposed Test Plan for American Chemistry Council Pyridine and Pyridine Derivatives Category
Physical/Chemical Properties

Chemical Name (CAS RN)	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient (log K_{ow})	Water Solubility
Piperidine (110-89-4)	A	A	A	A	A
Pyridine (110-86-1)	A	A	A	A	A
4-Picoline (108-89-4)	A	A	A	A	A
3-Picoline (108-99-6)	A	A	A	A	A
2-Picoline (109-06-8)	A	A	A	A	A
Pyridine, alkyl derivs. (68391-11-7)	**OECD 102**	**OECD 103**	**OECD 104**	**OECD 117**	**OECD 105**
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (68909-18-2)	**OECD 102**	**OECD 103**	**OECD 104**	**OECD 117**	**OECD 105**
Nicotinonitrile (100-54-9)	A	A	A	A	A
Picolinonitrile (100-70-9)	A	A	A	A	A

Note: Shaded areas represent adequate reliable measured data or adequate model data.
A = Adequate reliable data or model data exist.

Table 6
Proposed Test Plan for American Chemistry Council Pyridine and Pyridine Derivatives Category
Environmental Fate and Ecotoxicity

Chemical Name (CAS RN)	Photodegradation	Stability in Water	Transport & Distribution	Biodegradation	Acute Toxicity to Fish	Acute Toxicity to Invertebrates	Toxicity to Aquatic Plants
Piperidine (110-89-4)	A	NC	A	A	A	A	A
Pyridine (110-86-1)	A	NC	A	A	A	A	A
4-Picoline (108-89-4)	A	NC	A	A	A	A	A
3-Picoline (108-99-6)	A	NC	A	A	A	A	A
2-Picoline (109-06-8)	A	NC	A	A	A	A	A
Pyridine, alkyl derivs. (68391-11-7)	C	NC	C	C	A	A	C
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (68909-18-2)	C	NC	C	C	C	C	C
Nicotinonitrile (100-54-9)	A	NC	A	A	A	A	A
Picolinonitrile (100-70-9)	A	NC	A	A	A	A	A

Note: Shaded areas represent adequate reliable measured data or adequate model data.
A = Adequate reliable data or model data exist.
C = Endpoint fulfilled by category read-across from existing or proposed test data.
NC = Not calculable with the EPIWIN submodel and data development is not required since these types of chemicals are not hydrolysable.

Table 7
Proposed Test Plan for American Chemistry Council Pyridine and Pyridine Derivatives Category
Human Health-Related Data

Chemical Name (CAS RN)	Acute Oral Toxicity	Acute Inhalation Toxicity	Acute Dermal Toxicity	Repeated Dose Toxicity	Genetic Toxicity *In vitro*	Toxicity to Reproduction	Developmental Toxicity
Piperidine (110-89-4)	A	A	A	A	A	A	A
Pyridine (110-86-1)	C	A	A	A	A	**OECD 421** A	**OECD 421**
4-Picoline (108-89-4)	A	A	A	C	A	C	C
3-Picoline (108-99-6)	A	A	A	A	A	C	C
2-Picoline (109-06-8)	A	A	A	A	A	C	C
Pyridine, alkyl derivs. (68391-11-7)	A	C	A	C	C	C	C
Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides (68909-18-2)	A	C	C	C	C	C	C
Nicotinonitrile (100-54-9)	A	C	A	A	A	**OECD 421** A	**OECD 421**
Picolinonitrile (100-70-9)	A	C	C	C	C	C	C

Note: Shaded areas represent adequate reliable measured data or proposed testing.
Reliable data for acute toxicity by any of the three routes of exposure are adequate to fulfill the requirement for acute toxicity data.
A = Adequate reliable data exist.
C = Endpoint fulfilled by category read-across from existing or proposed test data.